UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

IN RE: NATIONAL PRESCRIPTION OPIATE LITIGATION, **THIS DOCUMENT RELATES TO:** *Track Three Cases*	**MDL 2804** **Case No. 1:17-md-2804** Judge Dan Aaron Polster

PLAINTIFFS' MEMORANDUM IN OPPOSITION TO DEFENDANTS' MOTION TO EXCLUDE CERTAIN OPINIONS AND TESTIMONY OF DR. KATHERINE KEYES

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INTRODUCTION

The Pharmacy Defendants ("Pharmacies") have moved to exclude certain opinions of Dr. Katherine Keyes, an expert epidemiologist, concerning (i) the causal connection between pharmaceutical "marketing" activities and the expanded access to and widespread availability of opioids; and (ii) the causal "gateway" effect that increased prescription opioid use has played in the rise in fentanyl use. Doc. #: 3858.[1] Besides insisting that Dr. Keyes' opinions should be barred as unreliable, the Pharmacies maintain that they would be unfairly prejudiced were the jury to hear them.

The Pharmacies make two arguments that Dr. Keyes' marketing causation opinions should be excluded, but neither is correct. First, they contend that Dr. Keyes' marketing opinions should be precluded for the same reason that similar opinions were precluded in CT1. That argument ignores that the record before this Court is substantially different from the record in CT1, and the analysis performed by Dr. Keyes was more robust and more firmly grounded in her epidemiological expertise. The Pharmacies' second objection to Dr. Keyes' marketing causation opinion, that Dr. Keyes did not examine their marketing, is similarly misguided. It was not necessary for Dr. Keyes to review the Pharmacies' marketing materials because she does not offer any opinions about their marketing. Rather, she provides background about the marketing of opioids generally that, when combined with other evidence, is probative of the Pharmacies' liability in this case.

The Pharmacies' attacks on Dr. Keyes' "gateway" causation opinions essentially rehash challenges that this Court rejected in CT1 and that Judge Faber rejected in CT2. Dr. Keyes' gateway causation opinions are based on the same exhaustive analysis of peer-reviewed studies as

[1] The Pharmacies do not challenge the remainder of the opinions disclosed by Dr. Keyes, and those opinions are therefore not at issue on this motion.

before, only amplified by her consideration of more recent studies and further articulation of the factors that lent particular strength to the studies upon which she relied. Aside from being meritless, the Pharmacies' quibbles with some of the studies upon which Dr. Keyes relied go to the weight of her opinions, not their admissibility.

Lastly, Dr. Keyes' opinion that increased prescription opioid use contributed to increased heroin and fentanyl-related harms does not prejudice the Pharmacies. Their unsupported complaints to this proffered testimony simply recycle other attacks. As with the Manufacturer and Distributor Defendants' challenge, this argument seeks to have the Court exceed its gatekeeping role. Because Dr. Keyes' opinions are methodologically reliable and anything but misleading, they are properly tested through the rigors of the adversary system at trial, where the Pharmacies will be free to cross-examine Dr. Keyes and offer any admissible countervailing evidence.

The Court should accordingly deny the Pharmacies' motion.

LEGAL STANDARDS

The applicable legal standards governing the Pharmacies' motion are set forth in Plaintiffs' Opposition to Certain Defendants' Daubert Motion to Exclude the Opinions Offered by James Rafalski, to which the Court is respectfully referred.

ARGUMENT

I. DR. KEYES APPLIED A RELIABLE METHODOLOGY TO SUPPORT HER OPINIONS THAT MARKETING ACTIVITIES THAT INCREASED OPIOID AVAILABILITY ARE CAUSES OF THE OPIOID EPIDEMIC

The Pharmacies' challenge to Dr. Keyes' marketing causation opinion plays a clever shell game. They start with a superficially appealing rationale for excluding Dr. Keyes' opinions on marketing causation—that because the Court did so in CT1, it must do so here. Mem. at 1, 5.[2]

[2] "Mem." denotes references to the Memorandum in Support of Defendants' Motion to Exclude Certain Opinions and Testimony of Dr. Katherine Keyes (Doc. #: 3858-2).

But tellingly, the Pharmacies do not attempt to argue that the actual reasoning of the Court's Order in CT1 applies to the opinions that Dr. Keyes offers in this case. Nor could they. Dr. Keyes has rectified the narrow and specific problem the Court identified in her prior report by reviewing and relying on additional studies that support her opinions, as an epidemiologist, on the role of marketing in increasing the prescribing and use of prescription opioids. She has also made more explicit her use of her epidemiological training and methodology in reaching her conclusion. Because Dr. Keyes' methodology and the record in CT3 are different from the methodology and record before the Court in CT1, the Court can and should reach a different conclusion about Dr. Keyes' marketing opinions than it reached there.

Next, the Pharmacies move the ball to another cup: they argue that Dr. Keyes' opinions on marketing causation should be excluded because she did not review materials on any specific marketing by the Pharmacies. But the Pharmacies concede that Dr. Keyes does not offer any opinions on their marketing and the Court need not exclude imaginary opinions. The Pharmacies then move the ball once again and argue that unless Dr. Keyes "evaluate[d] whether any Defendant engaged in any marketing and, if so, what type(s), what marketing materials were used, whether those materials were true or false, or whether those materials affected any prescriber's behavior," her opinions do not fit the case. Mem. at 10-11. There is no ball under this cup: it is "well established that a court may not exclude an expert's otherwise reliable and relevant testimony simply because, without more, the testimony is insufficient to prove a proponent's *entire* case." *United States ex rel. Landis v. Tailwind Sports Corp.*, No. 10-CV-00976 (CRC), 2017 WL 5905509, at *6 (D.D.C. Nov. 28, 2017) (citing cases; internal quotation marks omitted); *accord EEOC v. DHL Express (USA), Inc.*, No. 10 C 6139, 2016 WL 5796890, at *2 (N.D. Ill. Sept. 30, 2016) ("[T]he EEOC is not required to rely solely on DiPrete to prove their entire case."). Dr.

Keyes' opinion that opioid marketing expands the supply of prescription opioids is based on reliable principles and will inform the jury's evaluation of two crucial questions: (1) whether the Pharmacies were on notice of the need to guard against diversion, and (2) the causes of the opioid epidemic. The Pharmacies' demand that Dr. Keyes do more is without a basis in law.

A. The Court's Prior Reasoning for Excluding Dr. Keyes' Opinions Does Not Apply

In CT1, the Court observed that "[Dr.] Keyes clearly has specialized training and expertise in statistical analysis and the determination of factors that play a role in producing opioid-related harm." Doc. #: 2549 at 20. The Court, however, excluded Dr. Keyes' testimony about how pharmaceutical marketing caused an increase in opioid supply because Plaintiffs had "not shown that this expertise includes determining the effect of pharmaceutical marketing on doctors' prescribing practices." *Id.* at 21. In reaching this conclusion, the Court did not have before it evidence that Dr. Keyes is an investigator in a study analyzing, among other things, the effect of detailing (face-to-face meetings with physicians, either by pharmaceutical representatives as part of their marketing efforts, or by academic or public health physicians in an effort to combat the effects of drug-company marketing) on opioid prescribing habits. *See* Apr. 16, 2021 Keyes Report (Doc. #3852-7) ("Keyes Report") at 2 (discussing role in NIH-funded initiatives targeting opioid use). Additionally, as an epidemiologist, she has conducted large-scale survey data and vital statistics analyses, as well as the development of theories, hypotheses, and published findings concerning the role of macro-social factors in producing the opioid epidemic, including 28 peer-reviewed journal articles on opioid use and related harms. *Id.*[3]

[3] *See* Magdalena Cerdá, Yusuf Ransome, Katherine M. Keyes *et al*., *Prescription opioid mortality trends in New York City, 1990-2006: Examining the emergence of an epidemic*, 10 (Sept. 2013) (reporting "steps in the 1990s to increase the availability and use of analgesics, including aggressive marketing of potent formulations such as oxycodone hydrochloride and efforts to encourage clinicians to be more proactive in identifying and treating chronic pain," contributed to the opioid epidemic) (Ex. 1).

Although the Court found Dr. Keyes was not qualified to offer marketing opinions in CT1B, it did so because she had cited only a single study to support her conclusion, and she had not applied her epidemiological expertise in forming those opinions. Doc. #: 2549 at 20. In the absence of a more robust literature review, the Court reasoned that Plaintiffs "ha[d] not shown that [Dr. Keyes] applied epidemiological methods to determine that a cause-effect relationship may be inferred from the study that she cite[d]." *Id.*

Since her work in CT1, and in response to this Court's criticisms, Dr. Keyes reliably applied epidemiological principles to support her opinions on marketing causation and reviewed numerous peer-reviewed studies, not just one.[4] In her CT3 report, Dr. Keyes explained how she applied epidemiological methods to conclude that these additional studies support her opinion that marketing causes an increase in the opioid supply:

> Epidemiological evidence using statistical methods is routinely used to assess the association between exposure to pharmaceutical marketing and sales efforts with changes in prescribing, and has reliably found across many studies in many populations that exposure to pharmaceutical marketing and sales is significantly associated with increases in prescribing of the marketed drugs. Indeed, available epidemiological evidence using rigorous quasi-experimental designs, such as difference-in-difference models, as well as controlling for numerous potential confounders, has consistently documented an association between the industry payments, meals, sales outreach to physicians, as well as pharmaceutical promotions, with increases in requests to add specific products to hospital formularies as well as increases in rates of prescribing the marketed product.

Keyes Report at 33 (footnotes omitted). Dr. Keyes also performed an exhaustive analysis, based

[4] These additional studies include M.M. Chen & C.S. Landefeld, *Physicians' Behavior and Their Interactions with Drug Companies: A Controlled Study of Physicians Who Requested Additions to a Hospital Drug Formulary*, 271 JAMA 684-89 (1994); G.K. Spurling *et. al.*, *Information from pharmaceutical companies and the quality, quantity, and cost of physicians' prescribing: a systematic review*, 7 PLoS Med. E1000352 (2010); I. Larkin *et. al.*, *Association Between Academic Medical Center Pharmaceutical Detailing Policies and Physician Prescribing*, 317 JAMA 1785-95 (2017); and C. DeJong et al. *Pharmaceutical Industry-Sponsored Meals and Physician Prescribing Patterns for Medicare Beneficiaries*, 176 JAMA Intern. Med. 1114-22 (2016). *See* Keyes Report at 33 nn.135-39.

on the Bradford Hill factors,[5] of how these new studies integrate with the 2019 Hadland study she had relied upon in CT1 to create a "consistent evidence base" to support the conclusion that marketing of opioids increases the opioid supply. *Id.*

On this record, the rationale set forth in the Court's CT1 ruling is inapplicable here.[6] Unlike in CT1, Dr. Keyes did far more than cite a single report. She analyzed a body of literature using robust and widely accepted epidemiological principles and explained how it supports the sensible conclusion, from an epidemiological standpoint, that opioid marketing led to an expansion of the opioid supply. Indeed, it is telling that the Pharmacies make no serious effort to explain why the reasoning behind the Court's CT1 Order applies here—they spend two conclusory sentences asserting that it does before moving on to their other arguments. A closer look at those arguments, however, shows that the Pharmacies' challenge fails.

B. Dr. Keyes' Methodology Is Reliable and She Did Not Need to Review Marketing Material from the Pharmacies to Support Opinions She Is Not Offering

The Pharmacies simultaneously argue that (1) Dr. Keyes does not offer any opinions about specific marketing by the Pharmacies, and (2) any opinions she may have on specific marketing by the Pharmacies should be excluded because she did not review materials related to specific marketing by the Pharmacies. Mem. at 6-10. On its face, the latter argument is self-defeating.

[5] The Bradford Hill factors "guide epidemiologists in making judgments about whether a cause-effect relationship may be inferred from an association." *In re Welding Fume Prods. Liab. Litig.*, No. 1:03-CV-17000, 2005 WL 1868046, at *32 n.75 (N.D. Ohio Aug. 8, 2005); *accord In re Johnson & Johnson Talcum Powder Prods. Mktg., Sales Practices & Prods. Litig.*, 509 F. Supp. 3d 116, 161 (D.N.J. 2020) ("[C]onsideration of the Bradford Hill factors is a reliable method for determining causation."). As Dr. Keyes notes, although none of the individual studies that she cites, standing alone, establishes causality, application of the Bradford Hill factors to this body of literature as a whole does support causality. Keyes Report at 32. Remarkably, the Pharmacies completely ignore Dr. Keyes' analysis of the Bradford Hill factors in the marketing causation portion of their motion.

[6] Nor does Judge Faber's ruling in CT2 provide persuasive authority on this issue. Because Judge Faber's ruling was issued without an opinion, it is unclear whether he simply followed this Court's CT1 ruling, or if he did not, what the basis for his conclusion was. As of this date, he has not set forth the reasons for his ruling. *See City of Huntington v. AmerisourceBergen Corp.*, No. 3:17-cv-01362 (S.D. W. Va. Order filed Apr. 29, 2021) (ECF No. 1299).

There is no basis for excluding opinions that Dr. Keyes does not actually offer.[7] This portion of the Pharmacies' motion should be denied as moot.

As for the opinions that Dr. Keyes actually does offer on marketing causation, the Pharmacies' arguments for exclusion are unavailing. Dr. Keyes summarizes the consistent evidence that marketing *in general* increases the supply of prescription opioids and that the increase in the supply of prescription opioids here was caused, in part, by marketing *generally*. This is precisely because she is an epidemiologist, and thus is focused on *population-level* effects.[8] It makes no difference, for the purpose of Dr. Keyes' epidemiological analysis, *who* was doing the marketing that caused the increase. A population-level analysis of the effects of marketing on the opioid supply does not require analyzing marketing materials by the Pharmacies. The Pharmacies cite nothing—no epidemiological treatise, no case law, and no other authority—that suggests otherwise. Any objections to this testimony go to the weight, not the admissibility, of Dr. Keyes' testimony, and thus should be raised, if at all, during cross-examination.

C. Dr. Keyes' Opinions Fit This Case because They Provide Relevant Context on the Opioid Epidemic's Causes and the Pharmacies' Notice of Risk of Diversion

Next, the Pharmacies argue that, to the extent that Dr. Keyes' marketing opinions are not specific to the Pharmacies themselves, they do not "fit" the facts of this case. This argument fundamentally misapprehends—or mischaracterizes—the standard for the admission of expert

[7] The Pharmacies try to manufacture a dispute on this point by asserting that Dr. Keyes somehow offered different opinions from those contained in her report at her deposition. This is not the case. In both her report and her deposition, Dr. Keyes explained her opinions about marketing applied at the population level based on her review of the epidemiological literature and were not specific to any defendant. Doc. #: 3859-10 (Keyes Dep. at 106:4-8) ("I am not offering opinions about specific marketing activities of specific pharmacies or pharmacy chains. I am offering opinions about these articles in generality, in aggregate.").

[8] *See* Federal Judicial Center, *Reference Manual on Scientific Evidence* 551-52 (3d ed. 2011) ("Epidemiology is the field of public health and medicine that studies the incidence, distribution, and etiology of disease in human populations. . . . Epidemiology focuses on the question of general causation (i.e., is the agent capable of causing disease?) rather than that of specific causation (i.e., did it cause disease in a particular individual?).").

testimony. For an expert's testimony to "fit" the case, the proffering party need only show the expert "will testify to scientific knowledge that will assist the trier of fact in understanding and disposing of issues relevant to the case." *Pride v. BIC Corp.*, 218 F.3d 566, 578 (6th Cir. 2000).

As noted above, a court may not exclude an expert's otherwise reliable and relevant testimony simply because that testimony is insufficient to prove the proponent's *entire* case. *See supra* at 3 (citing cases).[9] The Pharmacies' bald assertion that unless Dr. Keyes "evaluate[d] whether any Defendant engaged in any marketing and, if so, what type(s), what marketing materials were used, whether those materials were true or false, or whether those materials affected any prescriber's behavior" her opinions should be excluded for lack of fit (Mem. at 10-11) has no basis in law.

Moreover, the Pharmacies' demand for exclusion misunderstands or mischaracterizes the role of marketing in this case. The Pharmacies were sued because, for decades, they were part of the pharmaceutical opioid industry that flooded Lake and Trumbull Counties with opioids by dispensing prescription opioids without reasonable, adequate controls against diversion, and thus contributed to a public nuisance.[10] Marketing—in which the Pharmacies participated in

[9] *See also* Fed. R. Evid. 702, advisory comm. note to 2000 amendments (expert can "educate the factfinder about general principles . . . without ever knowing about or trying to tie their testimony into the facts of the case"); *In re EpiPen (Epinephrine Injection, USP) Mktg., Sales Practices & Antitrust Litig.*, No. 17-MD-2785-DDC-TJJ, 2020 WL 1164869, at *6 (D. Kan. Mar. 10, 2020) (rejecting fit-based challenge to expert's testimony about "general background information about the pharmaceutical industry" because "Rule 702 allows this kind of generalized expert testimony").

[10] The Pharmacies' argument that Dr. Keyes did not consider conduct specific to each defendant in Lake and Trumbull Counties fails to acknowledge the Court has repeatedly rejected similar arguments. *See* Opinion and Order at 19 n.16 (Feb. 21, 2020) (Doc. #: 3177) (denying in part motions to dismiss TPP claims and allowing "Plaintiffs to use aggregate evidence to attempt to prove causation in the RICO context") (citing *In re Neurontin Mktg. & Sales Practices Litig.*, 712 F.3d 21, 46 (1st Cir. 2013)), reported at 440 F. Supp. 3d 773, 792 n.16; Order at 4 (Aug. 26, 2019) (Doc. #: 2542) (denying CT1 motion to exclude Cutler and noting "[t]he Court does not agree with Defendants that Cutler's reliance on aggregate [national] data undermines his opinions' fit with Plaintiff's theory"), available at 2019 WL 4011729, at *2; Order at 8-10 (Aug. 26, 2019) (Doc. #: 2531) (denying CT1 motion to exclude Gruber; rejecting "Gruber's omission of data on the bellwether counties in his quartile analysis as a reason to exclude his opinions"), available at 2019 WL 4011855, at *4-5.

collaboration with the manufacturers and distributors[11]—is relevant because it was a key factor in the pharmaceutical environment that helped create a flood of prescriptions for a highly addictive substance. As the accessibility and availability of prescription opioids increased, so did the risk and level of diversion that the Pharmacies could have and should have curtailed, but they failed to do so. Dr. Keyes' testimony, when viewed alongside documents presented through other witnesses that show the Pharmacies were aware that the manufacturers were engaged in aggressive marketing techniques[12] and marketed opioids aggressively themselves,[13] will help the jury determine that the Pharmacies were on notice of the need to create effective controls against diversion, which they then manifestly failed to do. Dr. Keyes' testimony about the origins of the increase in the supply of opioids will also inform the jury's evaluation of the multifaceted issue of causation, which the Pharmacies correctly observe is a "core issue" in this case. *See* Mem. at 11.

D. An Instruction That Dr. Keyes' Marketing Opinions Do Not Apply to the Pharmacies Is Both Unnecessary and Would Affirmatively Mislead the Jury

There is nothing unclear about the opinions Dr. Keyes actually offers—that opioid marketing increased sales and that opioid marketing led to the growth of the opioid supply. *See In re Zyprexa Prods. Liab. Litig.*, No. 04-MD-1596, 2008 WL 2696916, at *33 (E.D.N.Y. July 2, 2008) ("It is undisputable that expenditures for drug marketing increase sales. The billions spent by the pharmaceutical industry attests to that."), *clarified*, 2008 WL 2705475 (July 9, 2008). To

[11] At trial, Plaintiffs will present evidence of the Pharmacies' marketing and their collaboration with the Manufacturers. *See also* Pls.' Br. in Opp. to Defs.' Mot. to Exclude Anna Lembke § IV.

[12] *See, e.g.*, Ex. 2 (plea agreement in *United States v. Purdue Pharma L.P.*, Addendum A at ¶¶ 5-10, 17, 27-29, 81, 172-77, 181).

[13] *See, e.g.*, Ex. 3 (Walmart compliance manager observing, "You could Google Oxycodone or Suboxone and Sam's and they would tell you how to get these prescriptions filled at drastic savings. That is why many of these [illegitimate] scripts migrate to Sam's [C]lubs."); Ex. 4 (Walmart pharmacy manager writing that the company "really need[ed] to reevaluate our position on selling Tramadol [an opioid] for 4$" and expressed the view that "we are contributing to a bad thing by doing this").

the extent the Pharmacies wish to highlight that Dr. Keyes does not offer any opinions on their specific marketing, they will have ample opportunity to do so on cross-examination. A limiting instruction is thus unnecessary. Worse, a limiting instruction would run the risk of creating a false impression to the jury that the Court believes that the Pharmacies did not engage in marketing. This is, of course, untrue.

II. DR. KEYES' OPINIONS CONCERNING THE CAUSAL RELATIONSHIP BETWEEN PRESCRIPTION OPIOID USE AND SYNTHETIC OPIOID-RELATED HARMS ARE ALSO SOUNDLY SUPPORTED

The Pharmacies also contend that Dr. Keyes' opinion that "the use of prescription opioids is responsible for harms from illicit synthetic opioids" is not based on sound methodology. Mem. at 12. Defendants are wrong and this Court has already so found. Their argument essentially rehashes the Manufacturer and Distributor Defendants' CT1 challenge to the "gateway" causation opinions of Dr. Keyes and other experts (Doc. #: 1857) that this Court rejected, holding that those opinions are admissible. *See generally* Doc. #: 2518; *see also* Doc. #: 1868-4 (Dr. Keyes' Mar. 24, 2019 Report). The Court found that her opinions had a methodologically reliable foundation. Doc. #: 2518 at 10-12. The Pharmacies offer no persuasive argument that warrants this Court's reversal of its earlier ruling.[14]

A. Dr. Keyes' Methods Are Reliable

Dr. Keyes' methodology in her CT3 report mirrors that which she previously employed and which the Court deemed sound. *See id.* at 5-7 (finding that the experts appropriately relied on epidemiological literature). The Court noted that a report of the National Academies of Sciences, Engineering, and Medicine ("NASEM") had found that "the prescription and illicit opiate

[14] Plaintiffs note that, unlike the situation with Dr. Keyes' marketing causation opinion, the record with respect to "gateway" causation has only grown more robust. No changed circumstances warrant a different result here.

epidemics are intertwined," with "a majority of heroin users report[ing] that their opioid misuse or OUD began with prescription opioids." *Id.* at 6 (internal quotation marks omitted).

In her CT3 report, Dr. Keyes' opinions are only bolstered by her addressing earlier quibbles that some studies upon which she had relied have analyzed the transition from prescription opioids to heroin among subjects using prescription opioids "non-medically." *See* Keyes Report at 35-36. She has also addressed recent literature published since the preparation of her CT1 report, such as the 2020 McCabe, Mikosz, Tori, Gaines, and Cano & Huang studies. *See id.* at 23, 28, 35, 37-38.

Nevertheless, the Pharmacies attack Dr. Keyes' reliance on studies correlating heroin use with prescription opioid use as "reflect[ing] only a sequence of events" and lacking "even a theoretical basis for inferring causation." Mem. at 12-13. The Court, though. already found Dr. Keyes' methodology a reliable basis for her causation opinion. Doc. #: 2518 at 8-13. It concluded that the NASEM report, the Lankenau and Cicero studies, and Drs. Keyes' and Lembke's "first-hand clinical experience" provided ample support for the gateway trajectory of prescription opioid addiction leading to illicit opioid addiction. *Id.* Dr. Keyes' has now only amplified her conclusions, pointing to the 2020 McCabe study confirming that *every* possible sequence of prescription opioid use leads to increased use of heroin: medical use only (*i.e.*, used as prescribed by a physician); non-medical use only (*i.e.*, used outside of the parameters of a physician's prescription); medical use followed by non-medical use; and non-medical use followed by medical use. Keyes Report at 28, 37-38.

The Pharmacies maintain that "[n]one of the studies on which Dr. Keyes relies concludes that there is a causal relationship between prescription opioids and heroin, and they certainly do not posit that 70-80% of heroin use is 'attributable' to prescription opioid use." Mem. at 14. In her CT3 Report, though, Dr. Keyes cites published data "show[ing] that approximately 70-80% of

individuals who use[d] heroin in the last 20 years *started* their opioid use with prescription opioids." *Id.* at 36 (emphasis added). She notes that "the high-quality evidence across reviews indicates that the risk of incident opioid use disorders, as well as recurrence of opioid use disorders, increases in a dose-response fashion with the dose of opioids and the length of opioid use, even after controlling for individual-level predisposing factors[.]" *Id.* at 23.

Thus, as before, Dr. Keyes has applied a reliable methodology by relying on scientific studies to support her opinion that use of prescription opioids can, and does, lead to OUD, including nonmedical opioid use, and heroin/fentanyl use. Such extensive review of pertinent peer-reviewed literature provides a sound basis for an expert's conclusions.[15]

B. The Pharmacies Do Not Undermine Dr. Keyes' Reliability

In response, the Pharmacies cherry-pick a handful of the studies that Dr. Keyes discusses and then nitpick select findings therein. *See* Mem. at 13-14 & nn.14-17. They do so to the point of engaging in conjecture. *See id.* at 13 n.15 ("it is *quite possible* that the percentage overestimates the individuals who misused prescription opioids before heroin") (emphasis added). This selective parsing, however, does not go to the admissibility of Dr. Keyes' opinions but, rather, to the *weight*

[15] *E.g.*, *In re Heparin Prods. Liab. Litig.*, 803 F. Supp. 2d 712, 738 (N.D. Ohio 2011) ("Courts have admitted expert testimony as reliable where experts extrapolate their opinions from their knowledge and experience combined with a review of the relevant scientific literature."), *aff'd sub nom. Rodrigues v. Baxter Healthcare Corp.*, 567 F. App'x 359 (6th Cir. 2014); *Hardeman v. Monsanto Co.*, 997 F.3d 941, 967 (9th Cir. 2021) (expert's methodology underlying his conclusion was sound where, *inter alia*, he relied on "his clinical experience and reviewed scientific literature"); *Ferguson v. Lear Siegler Servs., Inc.*, No. 1:09cv635-MHT, 2012 WL 1058983, at *5 (M.D. Ala. Mar. 28, 2012) (expert's proposed testimony was "grounded in published peer-reviewed research"); *Tressler v. BNSF Ry. Co.*, No. CV-10-188-RMP, 2012 WL 315402, at *6 (E.D. Wash. Feb. 1, 2012) (expert's reaching her conclusions "by employing the technique of medical and scientific literature review and evaluation of available epidemiological data" was "a reliable methodology"); *In re Avandia Mktg., Sales Practices & Prods. Liab. Litig.*, No. 2007-MD-1871, 2011 WL 13576, at *9 (E.D. Pa. Jan. 4, 2011) (expert's opinions were "based on reliable scientific methodology (the review of peer-reviewed, published studies and data using well established statistical and scientific principles)").

that they should be accorded by the jury. Put another way, the Pharmacies' objections to some of the underlying studies may be fodder for cross-examination, but are not grounds for exclusion.[16]

At any rate, as noted above, the Court previously found that the Cicero and Lankenau studies "provide a sturdy basis" for Dr. Keyes' opinions, after evaluating those studies under the Bradford Hill criteria. Doc. #: 2518 at 11-12; *see supra* at 6 n.5 (citing cases). It rejected criticisms of the studies akin to those that the Pharmacies mount here, noting that reference to the low proportion of prescription opioid users who go on to use heroin was a red herring because the experts have not opined that most people who use prescription opioids become addicted to heroin but, rather, that most people who are addicted to heroin first used prescription opioids. Doc. #: 2518 at 11; *see* Keyes Report at 38 (noting that "[a] small but significant proportion of individuals who use prescription opioids progress to heroin use," but that "heroin use does not need to be common in order to be causally related to prior use of prescription opioids").[17] Defendants' short-sighted focus on the relatively small *percentage* of prescription opioid users also ignores the enormous impact in *absolute* terms: "Of note, given the large numbers of nonmedical users, even

[16] *E.g.*, *Bonner v. ISP Techs., Inc.*, 259 F.3d 924, 929 (8th Cir. 2001) ("As a general rule, the factual basis of an expert opinion goes to the credibility of the testimony, not the admissibility[.]"); *United States v. Bonds*, 12 F.3d 540, 561 (6th Cir. 1993) ("Disputes about specific techniques used or the accuracy of the results generated go to the weight, not the admissibility of the scientific evidence."); *United States v. L.E. Cooke Co.*, 991 F.2d 336, 342 (6th Cir. 1993) ("[A]ny weaknesses in the factual basis of an expert witness' opinion . . . bear on the weight of the evidence rather than on its admissibility.") (citing cases); *Deutsch v. Novartis Pharms. Corp.*, 768 F. Supp. 2d 420, 433 (E.D.N.Y. 2011) ("[O]bjections to expert opinions on the grounds that they are unreliable because they rely on non-controlled epidemiologic studies or extrapolate opinions from articles based on different cancer types than those of [plaintiffs] will not affect the admissibility of such opinions."); *In re Welding Fume Prods. Liab. Litig.*, 2005 WL 1868046, at *33 ("Given that no epidemiological study is flawless, in most cases, objections to the inadequacies of a study are more appropriately considered an objection going to the weight of the evidence rather than its admissibility. Vigorous cross-examination of a study's inadequacies allows the jury to appropriately weigh the alleged defects and reduces the possibility of prejudice.") (citation and internal quotation marks omitted).

[17] Also, as Dr. Keyes observes, that prescription drug use is neither necessary nor sufficient to predict heroin use does not mean there is no causal relationship. Noting that smoking is no less a cause of lung cancer simply because lung cancer is rare, Dr. Keyes cites evidence indicating that rates of heroin use increase with increasing amount of prescription opioids used. Keyes Report at 38. Based on the evidence, she found "a causal relationship between prescription opioid and heroin use, and that the increases in population-level heroin use in the United States are due, at least in significant part, to individuals who use prescription opioids transitioning to heroin use." *Id.* at 38-39.

a small percentage who initiate heroin use translates into several hundred thousand new heroin users."[18] As noted above, recent literature cited by Dr. Keyes confirms that *medical* users of prescription opioids also transition to heroin, which adds to the pool of heroin users arising from nonmedical use.

Furthermore, the Pharmacies sidestep many other of Dr. Keyes' observations—such as the high number of opioid prescriptions filled, significantly higher than in the 1990s, and increasing prescription length—and her consideration of numerous other systematic reviews or meta-analyses that assessed OUD among medical users of opioids (most notably the 2015 Vowles study), as well as her review of data from outpatient prescribing records. Keyes Report at 14-20. She also noted other studies—such as the 2014 Edlund study and a more recent McCabe study[19]—that, respectively, provided evidence of substantial risk of OUD after medical opioid use, and the transition of nearly one-third of nonmedical prescription opioid users in adolescence to heroin use. Keyes Report at 20-21, 37-38.

Based on "the high-quality evidence across reviews," Dr. Keyes concluded "that the risk of incident opioid use disorders, as well as recurrence of opioid use disorders, increases in a dose-response fashion with the dose of opioids and the length of opioid use, even after controlling for individual-level predisposing factors, and that 21-29% of chronic opioid users have mild, moderate or severe OUD." *Id.* at 23. She found the evidence "clear that risks of opioid use disorder following medical use of prescription opioids follow a 'dose-response' pattern," supporting a causal relationship between prescription opioid exposure and OUD. *Id.* at 23-24.

[18] Wilson M. Compton, *et al.*, *Relationship between Nonmedical Prescription-Opioid Use and Heroin Use*, 374 New Engl. J. Med. 154, 158 (Ex. 5).

[19] Plaintiffs previously discussed the Edlund study and earlier McCabe studies in connection with the Manufacturer and Distributor Defendants' 2019 motion to strike. Doc. #: 2197 at 16-18.

Far from ignoring "confounding factors" or disregarding "alternative explanations" (Mem. at 12),[20] Dr. Keyes articulated in detail the criteria that she used in selecting the literature upon which she relied. Keyes Report at 12-13.[21] With respect to confounding factors, Dr. Keyes specifically considered studies that had "a well-described strategy for statistical control of confounders," noting that statistical controls are necessary to overcome the potential for bias from confounding. *Id.* at 13. She noted that one study (the 2020 Powell study), which examined Medicare Part D prescription drug coverage as a potential driver of opioid use among those aged 65 and over, employed a design that specifically removed the possibility of confounding or increased risk factors as contributory drivers, and that the rigor of the 2019 McCabe study was enhanced by robust statistical control for confounding. *Id.* at 34, 37. In any event, like Defendants' other criticisms, an alleged failure to take confounding factors or alternative explanations into account is for the jury to weigh, not grounds for excluding expert testimony.[22]

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[20] As a threshold matter, existence of alternative explanations would not justify exclusion of Dr. Keyes' opinions. *E.g.*, *Bonner*, 259 F.3d at 929 ("[E]ven if the judge believes there are better grounds for some alternative conclusion, and that there are some flaws in the scientist's methods, if there are good grounds for the expert's conclusion, it should be admitted.") (internal quotation marks omitted; brackets added by court).

[21] Dr. Keyes looked to the rigor of the evidence used to support conclusions and opinions. With respect to studies that examine associations, she considered randomized controlled trials to be high-level evidence, but recognized that, for much of the literature she cited, randomized controlled trials would not be feasible or ethical for many of the associations reported, and she also noted the shortcomings in certain trials. *Id.* Where randomized controlled trials were not available, rigorous, or applicable to the issue of risk of OUD, Dr. Keyes considered meta-analysis and systematic reviews to be high levels of evidence because they assess the overall body of literature and provide quality assessments that weight evidence. *Id.* at 13. Specifically, she considered studies "that had prospective follow-up of patients or participants, a well-described strategy for statistical control of confounders, and well-designed comparison groups to be the next level of evidence," explaining her reasons for doing so. *Id.* Dr. Keyes also found studies of patient populations without comparison groups to be informative, particularly for research questions germane to the prevalence of opioid use disorders and related harm among patients prescribed opioids (especially high doses over a long duration), as well as questions related to the proportion of drug users who previously used prescription opioids. *Id.* With respect to studies that assess trends over time, she explained why she considered the highest levels of evidence to be (i) death records collected and harmonized by the national vital statistics surveillance system; (ii) data sources with a national reputation for transparency in reliability and validity that assess hospitalization and other clinical records; and (iii) survey data routinely collected in the general population of U.S. households over time. *Id.*

[22] *See Westberry v. Gislaved Gummi AB*, 178 F.3d 257, 265 (4th Cir. 1999) (expert's causation conclusion "should not be excluded because he or she has failed to rule out every possible alternative cause"; alternative causes suggested by a defendant "affect the weight that the jury should give the expert's testimony and not the admissibility of that testimony") (citing *Heller v. Shaw Indus., Inc.*, 167 F.3d 146, 156 (3d Cir. 1999)) (internal quotation marks

Ultimately, the Pharmacies' criticism of Dr. Keyes on this score is unavailing because she concluded that, if anything, "the existing evidence likely *underestimates* the total burden of opioid use disorders," noting that "existing studies routinely underestimate opioid use disorder," with fewer than half of substance use disorders identified in community samples even diagnosed or treated, "and thus a substantial portion, upwards of half, of total diagnoses are likely missed throughout studies that recruit and treat patients in medical settings." Keyes Report at 22 (emphasis added).

The Pharmacies further argue that, even if it is true that increased use of prescription opioids led to increased use of heroin, the causal chain cannot, as a matter of law, encompass the follow-on consequences arising from the adulteration of the heroin supply with fentanyl. Curiously, they cite no legal authority whatsoever for what they contend is a legal proposition. Mem. at 14-15. But even if Defendants were correct about the law—which they are not—Dr. Keyes does not offer opinions about *legal* causation. Rather, she is explaining the causal chain as a matter of fact—*i.e.*, what actually occurred. The Pharmacies may argue to the Court at an appropriate time that, by law, their legal responsibility does not extend down this causal chain, but that has nothing to do with the reliability or admissibility of Dr. Keyes' opinions, which will explain to the factfinder how the rising use of prescription opioids led first to increased use of heroin and later to increased deaths from adulterated heroin. The factfinder will then apply the law of causation and responsibility to this evidence as instructed by the Court.[23]

omitted); *Dugger v. Union Carbide Corp.*, No. CCB-16-3912, 2019 WL 4750568, at *5 (D. Md. Sept. 30, 2019) (asserted failure of epidemiological studies to take certain confounding factors into account was challenge "more appropriately brought before a jury").

[23] Besides, a task force of the Association of Schools and Programs of Public Health ("ASPPH"), a consortium of over 100 of the most reputable institutions of higher learning in the United States, issued a report that provides specific support for Dr. Keyes' opinion concerning the causal connection between prescription opioid use and transition to both heroin and fentanyl use. The report noted that "[t]he tremendous expansion of the supply of powerful (high-potency as well as long-acting) prescription opioids led to scaled increases in prescription opioid dependence,

The Pharmacies' additional argument that Dr. Keyes has not written about the relationship between adulterated heroin and prescription opioids (Mem. at 15) is beside the point. To begin with, Dr. Keyes has, of course, published on the "gateway" effect from prescription opioids to heroin. *See* Doc. ##: 2197-27, 2197-28 (2015 study and 2014 article). The gateway that Dr. Keyes has analyzed and expounded upon is prescription opioid use leading to use of illicit opioids. *Harms resulting from* illicit use are necessarily related. Dr. Keyes pointed to available evidence that fentanyl and other high-potency opioids have been adulterating the supply of both heroin and illicitly manufactured prescription opioids. Keyes Report at 39. Given her well-supported correlation of opioid use with heroin use, the increase in deaths from an adulterated heroin supply can logically be inferred from the rise in opioid use.[24] It is not necessary that Dr. Keyes have separately published concerning this particular inference. Indeed, the *Daubert* inquiry focuses on whether the *methodology* has been accepted in peer-review publications, not whether the expert's particular conclusions have ever been published.[25]

In sum, the Pharmacies' assertion that Dr. Keyes' cogent, well-substantiated opinions about the gateway effect rest "solely on her say-so" (Mem. at 16) is meritless.

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and the *transition of many to illicit opioids, including fentanyl and its analogs*, which have subsequently driven exponential increases in overdose." ASPPH, *Bringing Science to Bear on Opioids: Report and Recommendations from the ASPPH Task Force on Public Health Initiatives to Address the Opioid Crisis* at 8 (Nov. 2019) (footnotes omitted; emphasis added) (Ex. 6).

[24] *See Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 156 (1999) ("[N]o one denies that an expert might draw a conclusion from a set of observations based on extensive and specialized experience."); *Globetti v. Sandoz Pharms., Corp.*, 111 F. Supp. 2d 1174, 1176 & n.7 (N.D. Ala. 2000) ("If scientific methodologies can validate certain facts, scientifically reasonable inferences drawn from those facts are admissible."); *Perez v. Texas*, No. 11-CA-360-OLG-JES-XR, 2014 WL 12480146, at *3 (W.D. Tex. July 9, 2014) (expert's testimony "necessarily includes any inferences or deductions that the expert may draw from the information he has reviewed and analyzed").

[25] *See, e.g., Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 593-95 (1993) (listing as potentially useful factor whether "the *theory or technique* has been subjected to peer review and publication" and holding that "[t]he focus, of course, must be solely on principles and methodology, not on the conclusions that they generate") (emphasis added).

III. THE PHARMACIES' UNFAIR PREJUDICE ARGUMENT IS BEYOND THE SCOPE OF A FED. R. EVID. 702 MOTION

Finally, the Pharmacies assert that Dr. Keyes' gateway causation opinions should be excluded—or, in the alternative, followed by a limiting instruction—because they will "mislead and confuse the jury . . . causing unfair prejudice to Defendants." Mem. at 16.

As was the case with the Manufacturer and Distributor Defendants' CT1 motion to exclude Dr. Keyes' gateway causation opinions, this contention distills and recycles the Pharmacies' arguments concerning the admissibility of Dr. Keyes' opinions "in terms of the risk of misleading the jury." Doc. #: 2518 at 13; *see* Doc. #: 1858-1 at 16-17. Although Dr. Keyes would be opining on the correlation between the rise in prescription opioid use and increased heroin and fentanyl-related harms—*i.e.*, *factual*, not legal, causation—the Pharmacies do not want the jury to hear words such as "responsible" or "attributable." *See* Mem. at 16. That, however, is not a legitimate reason for barring Dr. Keyes' opinions. The Court should reject this argument for the same reasons as it did before.

A district court's role as a gatekeeper "is not intended to serve as a replacement for the adversary system." *Burgett v. Troy-Bilt LLC*, 579 F. App'x 372, 376 (6th Cir. 2014) (citing Fed. R. Evid. 702 advisory committee's note to 2000 amendment) (internal quotation marks omitted). Therefore, "[a] court should not use its gatekeeping function to impinge on the role of the jury or opposing counsel." *Id.* at 376-77. "As long as an expert's scientific testimony rests upon good grounds," as is the case here, "it should be tested by the adversary process—competing expert testimony and active cross-examination—rather than excluded from jurors' scrutiny for fear that

they will not grasp its complexities or satisfactorily weigh its inadequacies." *Ruiz-Troche v. Pepsi Cola of P.R. Bottling Co.*, 161 F.3d 77, 85 (1st Cir. 1998) (internal citation omitted).[26]

Thus, the Pharmacies "can present countervailing evidence and otherwise undermine [Dr. Keyes] through the adversarial give and take of a trial." Doc. #: 2518 at 14. The Court will, of course, instruct the jury, on the standards required to establish legal liability. Dr. Keyes' testimony, however, should not be foreclosed merely because she may use particular words attributing a causal relationship. Indeed, were that a proper basis for excluding or limiting expert testimony, much (if not most) expert testimony could not never be presented to a jury. Notably, the Pharmacies cite no case where a court excluded testimony because an expert used the specific words that irk them.[27]

[26] *Accord In re Se. Milk Antitrust Litig.*, No. 2:07-CV 208, 2010 WL 5102974, at *1 (E.D. Tenn. Dec. 8, 2010) ("[O]ur adversary system of justice presumes that the jury is capable of understanding the evidence; understanding and heeding the judge's instructions; and then separating the evidentiary wheat from the chaff[.]"), *R. & R. adopted*, 2011 WL 2693541 (July 11, 2011).

[27] Defendants muster one inapposite case. In *Woods v. Lecureux*, 110 F.3d 1215 (6th Cir. 1997), the Sixth Circuit upheld the refusal to allow, in a section 1983 action, an expert's testimony concerning whether prison officials' conduct amounted to "deliberate indifference," but that was given precedent that deliberate indifference is a precise legal term and was an ultimate issue in the case. *Id.* at 1219-21.

CONCLUSION

For the foregoing reasons, the Court should deny the Pharmacies' motion to exclude certain of Dr. Keyes' marketing and gateway causation opinions.

Dated: August 18, 2021

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